REMARKS

The Final Action mailed April 30, 2008, and the prior art there relied upon have been carefully studied. The claims in the application are now claim 1, 4, 7, 10, 16 and 21 - 25, and these claims recite novel and unobvious subject matter under Section s 102 and 103, whereby such claim should be allowed. Favorable reconsideration and allowance are respectfully urged.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

The present invention is based on the discovery by the present applicants/inventors that when granulocyte colony-stimulating factor (G-CSF) is administered as a drug or agent for the treatment of diabetes, stem cells in autologous bone marrow increase in number, and are recruited and differentiated into ß-cells in pancreatic Langerhans' islets. In addition, according to the present invention, it is unnecessary to administer bone marrow cells which are collected ex vivo. Furthermore, the physiological activity of G-CSF is so strong that inhibition of ß-cells disruption or regeneration of ß-cells in pancreatic Langerhans' islets can be confirmed.

Still further, it has been confirmed that a decrease in blood glucose level, which is the object of treating diabetes, can be produced by administration of G-CSF only.

The previous rejection based on Leschner et al has not been repeated, and applicants therefore understand that this rejection has been withdrawn.

New claims 23-25 have been added as dependent claims, and these are patentable at least for the reasons that they incorporate the subject matter of the claims from which they depend.

Claims 1, 4, 7, 10 and 15-20 have been rejected under Section 102 as anticipated by Hussain, previously applied against claim 1, 4, 7, 10 and 14-16. This rejection is again respectfully traversed for the reasons of record, respectfully repeated by reference, and for the additional reasons set forth below.

Hussain indicates that G-CSF or GM-CSF can be used for the treatment of diabetes. However, it is only GM-CSF that is actually used in the Examples and regarding which an advantageous effect can be confirmed. In other words, the term G-CSF merely appear once in paragraph [0010]. Thus, even one skilled in the art could not foresee based on the

disclosure of Hussain the advantageous effect of G-CSF brought about by the present invention.

In addition, Hussain does not at all describe the actual use of G-CSF. Therefore, Hussain does not even inherently or implicitly disclose the characteristic property of G-CSF according to the present invention. Hussain does not provide a disclosure which would enable one skilled in the art to reach applicants' claimed subject matter.

By the foregoing amendments, the present invention is specified as providing the effect of "granulocyte colony-stimulating factor differentiates autologous bone marrow cells *into* ß-cells". On the other hand, the method of Hussain requires "administering bone marrow derived stem cells" as an indispensable limitation. Therefore, the invention and disclosure of Hussain is quite different from the present invention in such indispensable feature.

Further, in Hussain, bone marrow derived stem cells are collected for administration. GM-CSF is used to recruit the collected bone marrow derived stem cells to differentiate them into pancreatic islet cells. Moreover, Hussain does not at all teach or suggest that G-CSF has the advantage of increasing the number of stem cells.

In comparison with Hussain, the present invention possesses characteristic features explained above. In other

words, the present invention is characterized in that (1) there is no need to collect stem cells after administration of a drug, and (2) to administer the collected stem cells to a diseased part, and also in that stem cells can be recruited by only the administration of G-CSF.

When the characteristic of G-CSF in the present invention is compared with the characteristic of GM-CSF in Hussain, it should be clear that the present invention is more effective for the treatment of diabetes than the process of Hussain. This is because the present invention does not need collection of bone marrow cells which the invention of Hussain does.

Therefore, the rejection of claims 1, 4, 7 and 16 based on Hussain should be withdrawn and such is respectfully requested.

As regards claim 10, applicants have noted above that, with regard to Hussain, it is only GM-CSF that is actually used in the Examples and in which an advantageous effect can be confirmed. Thus, Hussain does not at all disclose or suggest the advantageous effect of the present invention which is characterized by the use of G-CSF.

The inventors of the present invention discovered the surprising result that "inhibition of ß-cells disruption

and regeneration of ß-cells in pancreatic Langerhans' islets take place merely by administration of G-CSF, without bone marrow cells being transplanted". In addition, it was found based on this discovery that G-CSF can increase the number of stem cells in peripheral blood of bone marrow and then differentiate the increased stem cells into ß-cells. Therefore, the fact that G-CSF has the advantage of increasing the number of stem cells is a very important point to produce advantageous effects of the invention as claimed in claim 10.

As stated above, in Hussain bone marrow derived stem cells are collected for administration. GM-CSF is used to recruit the collected bone marrow derived stem cells to differentiate them into pancreatic islet cells. In other words, Hussain does not at all teach or suggest that G-CSF has the advantage of increasing the number of stem cells.

Claim 10 is not anticipated by Hussain and the rejection should be withdrawn. Such is respectfully requested.

Claims 1, 4 and 7 have been rejected under the first paragraph of Section 112 as failing to comply with the written description requirement. This rejection is respectfully traversed.

Applicants respectfully submit that this rejection must be based on having overlooked part of the disclosure of

the present specification. In this regard, attention is respectfully invited to applicants' specification at page 12, lines 18-25, where the following text appears:

> As shown in Example 1 and Figure 2, …. Thus, the agent for treating diabetes of the present invention is also effective as an agent for preventing ß-cells disruption in pancreatic langerhands' islets or an agent for **regenerating** ß-cells in pancreatic langerhands' islets. [Emphasis added]

Thus, "regenerating" is not new matter and clearly falls within the original written description.

Nevertheless, in deference to the examiner's views, some cosmetic amendments have been made in claims 1, 4 and 7. No changes in scope are intended by these amendments.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1, 4, 7 and 16-22 have been rejected under the second paragraph of Section 112. The rejection is respectfully traversed.

Although applicants believe that the person skilled in the art would not at all be confused about the language used in the rejected claims, nevertheless some minor cosmetic amendments have been to place the claims better form for U.S. practice. No added limitations are intended by these amendments.

For the record, to the extent that the rejection suggests or is intended to suggest that the advantageous effect of the present invention is dependent on whether the administration form is a composition or a drug or a pharmaceutical, applicants wish to strong traverse and refute any such suggestion. Thus, the advantageous effects of the present invention are produced by the administration of G-CSF regardless of whether the administration form is a composition or a drug or a pharmaceutical, assuming there is any difference; applicants understand such terms to be equivalent or substantially equivalent in the context in question.

Claim 1, 4, 7 and 16 have been rejected under Section 102 as anticipated by Okamura et al JP 2001/233784 (Okamura). This rejection is respectfully traversed.

As stated in the rejection, Okamura discloses the use of M-CSF, not the claimed G-CSF. Okamura does not anticipate any of applicants' claims.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1, 4, 7 and 16-20 have been rejected under Section 102 as anticipated by Brewitt et al USP 5,629,286 (Brewitt). This rejection is respectfully traversed.

Brewitt predicts which growth factors are efficacious for treating a disease such as diabetes and discloses a method for treatment of a disease by administering a growth factor as a homeopathic dilution.

As pointed out by the Examiner, Brewitt mentions an effective treatment for insulin-dependent and non-insulin dependent diabetes by using G-CSF as one of growth factors (column 6, line 37 to column 7, line 49). However, no working examples exist in Brewitt wherein G-CSF is administered to a diabetic patient (please refer to EXAMPLE 8, which is the only diabetes example). According to EXAMPLE 8 of Brewitt, when the LISTEN system is used, a growth factor of ßFGF, not G-CSF, was found to be most effective.

In addition, even in the case of ßFGF, it merely is said to be effective for the treatment of diabetes, but the advantageous effect of ßFGF is not actually confirmed. Brewitt does not provide a disclosure which would enable one skilled in the art in the art of use G-CSF

Therefore, the administration of G-CSF to a diabetic patient cannot be anticipated by Brewitt. G-CSF was not actually administered in the working examples of Brewitt. After all, G-CSF is not even judged to be effective in Brewitt.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1, 4, 7 and 16 have been rejected under Section 102 as anticipated by Krakowski et al, reference U (Krakowski). This rejection is respectfully traversed.

Krakowski at most only discloses a therapeutic effects of GM-CSF for the treatment of diabetes, subject matter which applicants are not claiming. In other words, Krakowski does not disclose applicants' subject matter, namely the use of G-CSF.

Withdrawal of the rejection is in or and is respectfully requested.

Claims 1, 4, 7 an 16-20 have been rejected under Section 103 as obvious from Lukic et al, reference V (Lukic) in view of Dalhoff et al, reference W (Dalhoff). This rejection is respectfully traversed.

As the rejection correctly states, Lukic does not disclose or teach G-CSF for the treatment of diabetes, and also does not disclose or teach that G-CSF differentiates autologous bone marrow cells into ß-cells. The rejection suggests, however, that Lukic teaches the following features:

(a) IL-1 has toxic and destructive effects against ß-cells (Lukic, page 122. right column, last paragraph).

(b) Treatment with IL-1 inhibitors (such as IL-1 receptor antagonist - IL-1 Ra) suppress development of diabetes (Lukic, Table II, page 126, concluding comments).

(c) Levels of the IL-1 Ra are increased after administration of G-CSF to human patients (abstract).

However, the present invention has the following particularly remarkable advantages that could not at all have been expected from the combination of Lukic and Dalhoff, even if their combination were obvious.

(i) When G-CSF is administered, autologous bone marrow derived stem cells are increased in number and recruited.

(ii) The stem cells recruited in (i) are differentiated into ß-cells in pancreatic Langerhans' islets.

(iii) The activity of (ii) has the advantage of inhibiting ß-cells disruption in pancreatic

Langerhans' islets which is caused by diabetes or regeneration of ß-cells.

(iv) The activities of (i) and (ii) are so strong that it is unnecessary to administer bone marrow cells which are collected ex vivo.

(v) Decrease in blood glucose level, which is the object of treating diabetes, actually takes place only by administration of G-CSF.

It is quite unclear whether the foregoing particularly remarkable advantages of the present invention can be produced only by the activity of increasing levels of IL-1 receptor antagonist. Applicants believe that advantages (i) to (v) obtained by the present invention are surprising effects that even one highly skilled in the art could not have expected from Lukic or Dalhoff or both considered together.

Moreover, applicants believe and respectfully submit that the proposed combination would not have been obvious to the person of ordinary skill in the art at the time the present invention was made. It takes a leap, the suggestion of which is only provided by applicants' specification, to bring the two references together in such a way as to result in the claimed subject matter. In addition, the prior art

even in combination, would not enable one skilled in the art to practice applicants' invention as claimed.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 10 and 15 have been rejected as obvious as under Section 103 from Lu et al, USP 6,610,535 (Lu) in view of Forbes et al WO 02/50263 (Forbes). This rejection is respectfully traversed.

Lu describes isolation of pancreatic progenitor cells (EXAMPLE 1) and induction of pancreatic progenitor cell differentiation (EXAMPLEB 2). Though various kinds of factors such as HGF, TGFß1 and IL-1α were used in these examples, G-CSF was not used. In other words, Lu does not at all disclose that G-CSF has the advantage of inducing pancreatic progenitor cell differentiation into ß-cells in pancreatic Langerhans' islets. Lu lacks enablement for the use of G-CSF as claimed.

As pointed out by the Examiner, Forbes discloses a method of collecting stem cells after administering a composition comprising G-CSF (page 22, lines 7-11). Forbes also teaches that the stem cells are further used in a patient in need of tissue repair as in the case of diabetes mellitus (page 19, lines 9-17). However, while stem cells can be collected by the teachings of Forbes, a concrete method of

tissue repair in a diabetic patient is not at all disclosed in Forbes, which only discloses regeneration of hepatic tissue by using bone marrow stem cells (Example 2. page 30, line 16 to page 37, line 12). Forbes does not describe regeneration of pancreatic tissue. In other words, Forbes does not at all disclose that G-CSF has the advantage of differentiating stem cells into pancreatic ß-cells. This advantage is one of the unobvious features of the present invention.

It is a surprising advantageous effect which the inventors of the present application found for the first time that administration of G-CSF makes it possible to increase the number of stem cells and to differentiate the thus obtained stem cells into ß-cells in pancreatic Langerhans' islets.

Moreover, applicants believe and respectfully submit that it would not have been obvious to a person of ordinary skill in the art at the time the present invention was made, without recourse to applicants' specification, to bring the two references together and somehow begin to even approach the claimed subject matter. Consideration of the two references together would not enable a person skilled in the art to practice applicants' method.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 21 and 22 are rejected under Section 103 as obvious from Hussain in view of Bonhomme et al USP 6,303,146 (Bonhomme). This rejection is respectfully traversed.

The deficiencies of Hussain have been pointed out above and previously with respect to claims 1, 4, 7 and 17, and the same points apply with respect to claims 21 and 22. Bonhomme has not been cited to make up for the aforementioned deficiencies of Hussain, and indeed does not do so.

The present invention possesses characteristic features explained above. In other words, the present invention is characterized in that no step is required for collecting stem cells after administration of a drug and for administering the collected stem cells to a diseased part, and in that stem cells are recruited simply and only by administration of G-CSF.

In contrast to the present invention, the method of Hussain requires "administering bone marrow derived stem cells" as an indispensable requirement. In addition, neither Hussain nor Bonhomme disclose or suggest that G-CSF has the advantage of increasing the number of autologous stem cells.

Even if Hussain were to be combined with Bonhomme (which applicants do not accept would have been obvious), the characteristic feature that "autologous stem cells are increased in number and recruited" without "bone marrow

derived stem cells being administered" could not have been conceived by a person having ordinary skill in the art at the time the present application was filed. Therefore, applicants do not agree that claims 21 and 22 would have been obvious from Hussain in view of Bonhomme. Claims 21 and 22 should be allowed.

The inventors of the present application found, for the first time, the surprising results that autologous bone marrow derived stem cells are recruited by administration of G-CSF without administering bone marrow cells which are collected ex vivo, and that as a result, inhibition of ß-cells disruption and regeneration of ß-cells in pancreatic Langerhans' islets are produced. These results are not taught or suggested by Hussain or Bonhomme. Thus, it should be accepted that they are particularly remarkable unobvious advantages.

Withdrawal of the rejection is in order and is respectfully requested.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that should lead to patentability. Favorable reconsideration and allowance are respectfully requested.

Respectfully submitted,

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